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THE HOWE LABORATORY AND DEPARTMENT OF OPHTHALMOLOGY

HARVARD MEDICAL SCHOOL

AT THE

MASSACHUSETTS EYE AND EAR INFIRMARY

1966

243 CHARLES STREET

BOSTON, MASSACHUSETTS

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TEMPORARILY ATTACHED TO THE LABORATORY

Special Fellowships:

William M. Haining, M.D.: *E. B. Dunphy Fellowship and USPHS (Center Grant)*
Robert S. Hepler, M.D.*: *USPHS*

* Transferred to another institution during 1966.

(Continued on inside back cover)

Forty years ago Dr. Lucien Howe offered the sum of $250,000 to Harvard University on a matching basis for the establishment of an ophthalmic research laboratory. Equivalent funds were provided by the General Education Board of the Rockefeller Foundation, and the Howe Laboratory came into being. So far as we are aware this was the first endowed ophthalmic research in the United States. It provided a then unique opportunity for investigators to make ophthalmic research a career.

Later by four decades, one world war, and after numerous socio-economic and scientific changes, the Howe Laboratory continues to offer extraordinary, if no longer unique, opportunities for qualified persons who seriously wish to dedicate their lives or funds to research on the eye. The research emphases have changed over the years but, as recorded in these Annual Reports, have maintained an obvious line of continuity and, we believe, productivity. The persistent theme has been consolidation of basic and clinical sciences pertaining to the eye.

We are no longer topmost in financial support and we have much less space than many other ophthalmic laboratories in this country but we have deep roots, loyal supporters, and a determination to maintain high standards of research output. We are able to record each year modest but solid advances and we are grateful for the opportunity of sharing in the humanitarian, cultural, and scientific satisfactions that go with ophthalmic research.

RESEARCH ACTIVITIES

Glaucoma

The recognition and treatment of glaucoma are of such pressing importance, with one or two out of every hundred adults affected and more than 30,000 in this country blinded by the disease each year, that inevitably the clinical problems determine the main direction of research.

Alcohol and pituitary hormones

The mechanism by which the pressure in glaucomatous eyes is lowered by alcohol has been investigated further by Drs. Grant and Roland E. Houle. With the help of patients who volunteered their

cooperation in these studies, an investigation was made of the possible role of the antidiuretic hormone, which in human beings is known to be suppressed by alcohol and to cause a change in the water balance of the body, possibly affecting the intraocular pressure indirectly. Dr. Houle confirmed that alcohol lowered the intraocular pressure of glaucomatous patients, and found that this effect could be partially or completely prevented by simultaneously administering a dose of hormone which by itself had no influence on intraocular pressure. This seemed to support the idea that the body's own supply of the hormone played a part in regulation of the pressure. Further investigation, however, of patients with pathologic excess or deficiency of the hormone, because of abnormalities of the pituitary gland, indicated that this particular hormone plays only a small role in regulation of the intraocular pressure. This was best demonstrated in an individual who completely lacked antidiuretic hormone on account of previous pituitary ablation, and had glaucoma in one eye induced by repeated application of a cortisone-like drug; a fall in the intraocular pressure was produced in this patient's glaucomatous eye by alcohol just as in patients with normal pituitary glands.

Antiglaucoma drugs

Research on drugs for use in treatment of glaucoma requires study of possible adverse effects as well as of potential benefits. After adequate testing in the laboratory the ultimate evaluation must be done with the cooperation of patients since one cannot expect to rule out all adverse effects by preliminary animal experiments.

Now certain of the miotic drugs which have earned a place as valuable agents for reducing the pressure in glaucoma are being suspected of causing opacities in the lenses. This is not easy to be certain about without careful study, because many glaucomatous patients develop cataracts regardless of the type of treatment. Careful observation on patients by Dr. Thoft and on lenses of animal eyes by Drs. Michon and Kinoshita are being carried out to determine the frequency, severity, and pathogenesis of these complications. Two of the more popular anticholinesterase agents, Humorsol and Phospholine Iodide, have been found experimentally to cause vacuoles at the lens surface; in animal eyes Humorsol affects pri-

marily the anterior surface, Phospholine Iodide affects chiefly the posterior portion of the lens. The lens changes depend on the dose and duration of treatment.

Biochemically these agents cause a marked increase in permeability of the lenticular membranes while sparing the cation pump mechanism. In addition, Humorsol compromises oxidative metabolism of the lens. At much lower concentrations these agents inhibit the cholinesterase earlier demonstrated to be present at the lens surface.

Surgery in glaucoma

Relief of glaucoma by surgery varies widely in its ease and effectiveness depending on the type of glaucoma. In the early stages of so called angle-closure glaucoma, a complete cure is usually assured by iridectomy. In congenital glaucoma, if diagnosed early enough in infancy, control is achievable surgically by goniotomy in better than 80 percent. At the other extreme is neovascular glaucoma, in which relief either by medical or surgical treatment is rare. At a clinical level, systematic studies are being made of pathologic conditions leading to neovascular glaucoma by Dr. David Walton, of the details of the course of development of this type of glaucoma by Drs. Thoft and Jose Peczon, and of novel means of surgical management by Drs. Ernst Meyer and Grant and members of the resident staff.

In the laboratory, Drs. Brubaker and Worthen are currently making a systematic and controlled study of the surgical factors which influence drainage of aqueous humor in the monkey eye. One type of surgery aims to produce an artificial route of drainage for this fluid from the inside of the eye to circumvent the natural outflow channels which become obstructed in disease. The greatest obstacle to the success of this type of surgery is a tendency to healing and closure of the artificial drain. This tendency varies greatly from one patient to another. Certain modifications of technique and associated means of treatment which are clinically feasible are being explored in otherwise hopeless cases.

Congenital glaucoma

The glaucomas of infancy and childhood continue to be a particular concern of Dr. Grant and he has continued to participate in

the examination and treatment in the majority of patients with this disease seen at the Infirmary, collecting data to serve as a guide for future management and as a basis for modification of treatment currently being introduced from time to time. Most recently, because Dr. Grant has been impressed with progressive changes in the angle and progressive worsening of glaucoma in certain aniridic patients during childhood, early goniotomy has been employed in hopes of preventing or minimizing the development of glaucoma. A contribution to technique of goniotomy has been made in the form of a tiny sterilized focused light controlled directly by the surgeon to illuminate specifically the area of the angle of the anterior chamber which is being operated upon, minimizing surface reflections and glare.

Capsular glaucoma

Dr. Hørven pursued the subject of "capsular glaucoma," that is the type of glaucoma in which particulate material appears to come from the lens capsule and to obstruct the out-flow channels. In Norway, whence Dr. Hørven comes, capsular exfoliation is reported to be present in 80–90 percent of all cases of open angle glaucoma whereas Dr. Hørven found it present in only 28 percent of a series of glaucomatous patients at the Massachusetts Eye and Ear Infirmary. This is higher than has been previously reported in the United States but still less by far than that occurring in Norway.

Experimental Pathology

Retinal vasculature

The studies on retinal vasculature which were made possible by Dr. Kuwabara's discovery of the trypsin digest method have been more energetically pursued this past year by other laboratories than by the Howe Laboratory. With our severe space limitations we have had to decide between emphasis on these histologic observations or on electron microscopy. We chose the latter. Although we continue to accumulate routine specimens and occasionally to make a special study of selected cases, our chief activity in the field of retinal vasculature this past year has been that of commentators and reviewers. Similarly in the field of diabetic reti-

nopathy our activity this past year has concentrated on the preparation of review and text material with the aim of consolidating and analyzing the many observations that we and others have made with the trypsin digest method.

Retinal damage by visible light

With increasing intensities of artificial light sources, a recurrent question from lay as well as from scientific groups has been the limit of safety to the eye. Intensities above that of thermal coagulation will, of course, produce chorioretinal burns but until this past year we have felt secure in the belief that all ordinary sources of illumination were harmless. When Dr. Werner Noell of Buffalo reported that continuous exposure of mice to banks of 30 watt fluorescent lamps caused these animals to become blind we were skeptical. But Dr. Kuwabara repeated the experiments on rats and has confirmed and extended Noell's observation. With Dr. Gorn he has continuously exposed groups of albino rats to fluorescent illumination of 1,000 foot candles and found a decrease in the electroretinographic response within a few hours. The animals are totally blind within a week. On being replaced in the dark the animals may recover completely but longer exposures result in irreversible blindness.

Electron microscopy of the light damaged retinas show the site of the lesion to be in the outer segments of the rods. The laminated plates first swell and take on the appearance of vacuoles. The plates then lose their regular arrangement; they fragment and eventually disappear. With the loss of the whole outer nuclear layer the retinas resemble those of photoreceptor abiotrophy. Recovery is characterized by reappearance of the laminated plates.

The intensity of 1,000 foot candles is brighter than most artificial illuminations to which we are customarily exposed but considerably less than the illumination of outdoor sunlight and is estimated to be only 0.5 percent of the energy necessary to cause photocoagulation of the retina. Although albino rats were used in the experiment, blindness has been similarly induced in pigmented animals and in chickens exposed to continuous illumination. This latter is especially interesting since chickens, in contrast to rats and mice, have all-cone retinas.

There is no evidence that exposure of man to continuous high

illumination from ordinary artificial sources will cause permanent visual loss but these experiments give cause to wonder, and alert us to this possibility. Needless to say the subject is being vigorously pursued both in our Laboratory and in other laboratories.

Iodoacetate poisoning

For the past several months Dr. Kuwabara and his staff have been studying the effects of experimental iodoacetate poisoning on the retina. This has turned out to be important from several points of view. In the first place, iodoacetic acid has long been known to produce selective degeneration of the rod and cone layer and has therefore been interpreted as the experimental counterpart of retinitis pigmentosa in human beings. Contrary to this interpretation, however, Dr. Kuwabara finds that the target site is not in the photoreceptive portion of the rods and cones as is the case with retinitis pigmentosa but at the synaptic junction with the bipolar cells. More specifically, the neurophysiologic (electroretinographic) and anatomic (electron microscopic) evidence points to a primary alteration in the horizontal cells and in their connections at the bipolar-photoreceptive synapses. It appears that the processes of the horizontal cells normally envelope the bipolar dendrite and that iodoacetic acid causes a retraction and disintegration of these processes with secondary degeneration of the rod and cone cells. The major importance of these observations is the lead which they give, for the first time, as to the morphological and functional significance of the enigmatic horizontal cells of the retina.

Myelin artifacts

We have again documented our observations on myelin artifacts. These artifacts, first described by Drs. Cogan and Kuwabara several years ago, result from forward squeezing of myelin into the peripapillary region at the time of enucleation. Because of their mass these myelin artifacts have been misinterpreted as tumor. They sometimes also insinuate into the retinal veins and have been misinterpreted, we believe, as emboli. Awareness of the artifacts is therefore important for the ophthalmic pathologist. We have now presented some evidence suggesting that an analogous forward squeeze of myelin into the nerve head or vitreous may occur during

life in occasional cases of papilledema from orbital masses and following blunt injuries to the eye.

Ophthalmic Biochemistry

Cataracts

The working hypothesis that has evolved from the studies on galactose cataracts by Dr. Kinoshita, Dr. Thoft, and Mr. Merola is that accumulation of dulcitol creates an osmotic imbalance within the lens fibers. If this sugar alcohol-osmotic theory is correct other changes which occur early in cataract development should be related either to the accumulation of sugar alcohol or to the concomitant increase in lens hydration. One of these early changes is an increase in sodium (Na) and decrease in potassium (K) in the lens. Excessive influx of sodium and concomitant increase in chlorine (Cl) leads to marked swelling of the lens. The lens normally excludes sodium by a cation pump and one explanation for the abnormal Na accumulation in the lens might be an interference with the pump mechanism caused by the build up of sugar alcohol concentration. Dr Kinoshita and his group, however, find the rate of cation turnover is increased rather than decreased in the early stage of galactose cataract formation, indicating that the rates of cation uptake and exit are both accelerated. The changes in K fluxes are similar to those of Na but in the opposite direction. Thus early in cataract formation K efflux increases but the lens compensates for this by accelerating the cation pump to increase K influx. The lens is thereby able to offset the increased cation permeability – that is, until a point in cataractogenesis is reached when the cation pump can no longer keep pace with the increasing cation permeability. There is then a net gain of Na and loss of K.

The initial increase in cation permeability appears to result from the lens swelling caused by dulcitol. The evidence for this comes from the experiments *in vitro* in which rabbit lenses are incubated in high levels of galactose. These lenses if allowed to swell show an increase in cation turnover similar to that observed in the lenses of rats fed galactose. But *in vitro* the lenses can be kept from swelling despite the accumulation of dulcitol by increasing the tonicity of the bathing medium during incubation. Under these conditions, the rate of cation uptake and that of cation

exit are kept within normal limits. It thus appears that it is the swelling which results from the retention of dulcitol, rather than some toxic action of dulcitol, that is responsible for the increase in permeability to cations. Therefore, the sugar alcohol-osmotic theory does offer an explanation for the changes in cation levels during the development of a galactose cataract.

Enzymes and rate limiting factors

Crucial to an understanding of lens biochemistry is an understanding of those enzymes concerned with glucose metabolism. Drs. Lou and Kinoshita have directed especial attention to the regulation of glycolytic enzymes present in the lens. Because hexokinase occurs in the lowest concentration many investigators have regarded the hexokinase reaction as the rate limiting mechanism in lens glycolysis. A closer examination of this initial phase of glycolysis has revealed, however, a complex set of circumstances involving substrate and product inhibitions of two key enzymes, hexokinase and phosphofructokinase (PFK). One controlling mechanism is the PFK reaction in which adenosine triphosphate (ATP) and fructose-6-phosphate are the substrates. Purified lens PFK is inhibited by elevated concentrations of ATP. The inhibition of this reaction raises the concentration of fructose-6-phosphate which is immediately converted to glucose-6-phosphate, the product of the hexokinase reaction. Studies with isolated preparations of lens hexokinase have revealed that this enzyme is sensitive to excess glucose-6-phosphate. Increasing levels of glucose-6-phosphate leads to marked inhibition of lens hexokinase. The interesting aspect of these delicately controlled reactions in the lens is that normal levels of ATP and glucose-6-phosphate are at concentrations where some degree of inhibition would be exerted on each of the two enzymes. In reconstructing the sequence of events that occur in the intact lens it appears that when sufficient ATP is available the rate of lens glycolysis is not operating at maximum. This is explained by the ATP inhibition of the PFK reaction which in turn increases the glucose-6-phospate level sufficiently to depress the hexokinase reaction. On the other hand a depressed level of ATP would accelerate the PFK reaction which in turn lowers the glucose-6-phosphate level thus stimulating the hexokinase reaction and consequently increasing the rate of glucose utilization. These key enzymes in

the lens seem peculiarly sensitive to small changes in ATP and glucose-6-phosphate levels and provide the lens with a sensitive and precise mechanism for regulation of glycolysis. This appears essential because unlike most tissues the lens depends on glycolysis as the primary source of energy. Lactic acid is then the principal end-product of metabolism. The glyoclytic mechanism must, therefore, provide the lens with sufficient biological energy in the form of ATP, but also must not allow excessive quantities of acid to accumulate.

Radiation cataracts

Work was begun this year by Dr. Lambert under the direction of Dr. Kinoshita on the pathogenesis of radiation cataracts. X-radiation of rabbit lenses in doses of 500 to 6000r was shown to affect primarily lens membrane integrity as measured by an increased rubidium ^{86} efflux. At the same time active transport as measured by rubidium ^{86} uptake was unaffected. Further studies are in progress to elucidate the relationship between these permeability changes and the posterior subcapsular cataracts found with exposure to ionizing radiation.

Corneal metabolism

A study of the metabolism of the various layers of the cornea was undertaken by Dr. Andrews. The rate of metabolism of the intact calf cornea was found to be twice that of the sum of the separated epithelium and stroma. Results of this type of experiment have been cited as evidence for the possible metabolic interactions between the epithelium and stroma. Dr. Andrews has found that injury, incurred by the epithelium during the separation of the cell layer from the stroma, may complicate the interpretation of these findings. Using a typical soluble enzyme, glucose-6-phosphate dehydrogenase, as an example, he was able to demonstrate that considerable quantities of this enzyme diffused into the medium during incubation of the epithelium obtained from scraping the cornea with a scalpel. In contrast, very little loss of the enzyme was observed during the incubation of an intact cornea. Apparently, more subtle incubation procedures will have to be devised before a definitive study on the possible metabolic interactions between epithelium and stroma can be realized.

Electron microscopic studies have revealed that mitochondria of the corneal epithelium are much smaller and contain less well defined cristae than mitochondria of other tissues. A subject of investigation by Dr. Andrews was whether these differences are reflected in the ability to metabolize intermediates of the Kreb cycle. Dr. Andrews found that isolated mitochondria from calf corneal epithelium were able to oxidize succinate to carbon dioxide to some extent, but that addition of soluble cytoplasmic components to the mitochondrial preparation greatly stimulated the succinate oxidation. Comparative testing of liver mitochondria showed much less response under similar circumstances. The identification of the factors in the cytoplasmic fraction of the corneal epithelium has not been completed, but it appears that a protein component, presumably an enzyme, is responsible for the stimulating effect.

Fatty acids of the retina

The synthesis of fatty acids in the retina has been found to occur in the microsomes and in the supernatant fluid obtained by ultracentrifugation of retinal homogenate. Dr. Futterman found that the microsomes convert malonyl CoA to all of the long chain fatty acids which occur naturally in vitamin A esters. In addition the microsomes were found to carry out sequences of chain elongation and introduction of double bonds which result in the synthesis of arachidonic and docosahexaenoic acids. These fatty acids, although not found in vitamin A esters are major constituents of the retinal lipids. The microsomes are capable of esterifying vitamin A by using either the fatty acids which they synthesize or those which are synthesized by the supernatant fluid fraction of retinal tissue homogenate.

Neuro-ophthalmology

Congenital ocular motor apraxia

The entity of congenital ocular motor apraxia has been of interest to us since we first described it 15 years ago. Fourteen cases have now been described in the literature and eleven further cases are known to us in addition to the four we originally described. Believing a re-evaluation of the syndrome was in order we have analyzed the 29 cases and have come to the following conclusions:

The entity occurs in boys about twice as often as in girls. Some evidence suggests an autosomal recessive mode of transmission. The lack of ocular fixation often leads to the erroneous impression of blindness in the early months of life and sometimes to extensive neurologic and neurosurgical investigation. Children with this entity are characteristically clumsy in their physical activities and are poor readers in school but have no regularly associated neurologic deficiency. The condition improves in the first and even in the second decade of life. This improvement probably accounts for the fact it has not been recognized in the adult.

Congenital nystagmus

Believing that the pathogenesis for the various types of congenital nystagmus was not widely appreciated we collated approximately 100 cases and found that the majority could be categorized into either (1) a sensory-defect type in which an abnormality of the macular function deprived the eyes of a proprioceptive stabilizer or (2) a motor-defect type in which the pathways which subserved the horizontal optokinetic response were not fully developed. Vision was, of course, poor in the former but normal in the latter so long as the eyes could be turned to a position of relative rest. Latent nystagmus was a less common variant of congenital nystagmus and periodic alternating nystagmus was the rarest type of all.

Electroretinography and evoked occipital potentials

Means for measurement of light induced signals from the retina and from the occiput have been further developed by Dr. Fricker using his Synchronous Detector equipment. Data has been accumulated on time-delay and amplitude in normal and abnormal subjects. Normal retinal signals have a delay of approximately 24 milliseconds and it requires extensive damage or malfunction of the outer retinal layers to alter this delay time significantly. Signal amplitudes show more variations than delay times among individuals but are approximately identical in the two eyes of any one subject. The delay times and signals recorded from the occipital area show a wider range of "normal" than those from the retina with correspondingly greater difficulty in evaluating the possibly abnormal responses. On the other hand, unilateral abnormalities of macular function can be usually detected by comparison of the

responses from the two eyes or by a decreased delay time at higher frequencies. Work along these lines will be considerably facilitated in the coming year by use of a multi-channel data tape recorder that will permit simultaneous recording of several parameters of measurement.

Inborn metabolic disease

Ocular correlates of inborn metabolic disease were reviewed by Dr. Cogan in an address to the Canadian Medical Association. Because of our close ties with the Children's Hospital and the Massachusetts General Hospital we have had an unusual opportunity to see and study a variety of patients with metabolic disease in which characteristic deposits or opacities occur in the transparent media of the eye. These include deposits in the cornea (cystinosis and several types of mucopolysaccharidosis), in the sclera (alcaptonuria), opacity of the lens (galactosemia) and deposits in the retina (Tay-Sachs disease and other sphingolipidoses). The ophthalmologist can play an important and sometimes crucial role in the diagnostic and prognostic evaluation of patients with these metabolic abnormalities.

Passive mobility of the eye

Failure of an eye to move properly may result from either a paralysis of a muscle or a fibrous band holding the eye in place. It is often impossible to differentiate these two by simple clinical observation and one common method is to estimate resistance to movement by "forced duction" accomplished by attempting movement of the eye by means of forceps. This, however, is a cumbersome and sometimes painful procedure. Drs. Reinecke and Stephens have developed a new and relatively simple system that holds considerable promise. A suction contact lens is placed on the eye and that force measured which is necessary to rotate the eye a predetermined amount.

Fluorescein angiography

Through the generosity of the Massachusetts Lions Club (E. B. Dunphy Fellowship) and ancillary assistance from the NIH Center Grant, we have been able to participate in exploration of fluores-

cein angiography of the retinal vessels. Dr. Haining, Senior Registrar of the University of Edinburgh, has joined the Laboratory for a year. His considerable experience in this field and the past experience of the Howe Laboratory in the retinal vasculature makes this a natural liaison which should yield valuable information in this clinically important field.

Transneuronal atrophy

Extending his studies on transneuronal atrophy in the lateral geniculate body, Dr. Kupfer found that inhibition of functional activity of the optic nerve by means of long acting local anesthetics reduced the metabolic activity of the geniculate neurones. But it did not decrease the size of the cells as did surgical section of the optic nerves. These findings suggested to Dr. Kupfer and to his collaborator, Dr. John Downer (University of London), that the metabolic activity of the geniculate neurones was related to neural activity of the optic pathways whereas atrophy depended on anatomical changes in the synapse between the optic nerves and the geniculate bodies.

Ocular oscillations and truncal ataxia

In conjunction with members of the Neurology Service at the Massachusetts General Hospital we have identified this past year a syndrome characterized by intermittent ocular oscillations and truncal ataxia associated with a transient encephalitis. The oscillations are rapid, intermittent, and often associated with voluntary movements of the eyes. The movements are predominantly horizontal and may vary from two to twelve or more before coming to a standstill. They occur with the eyes open or shut and are totally involuntary. The disease is incapacitating. The patients cannot sit up or stand without support, and their vision is disturbed. Nevertheless the disease is benign and resolves completely within a few weeks.

This entity which we have tentatively called "Ocular Oscillations and Truncal Ataxia" differs from ocular motor dysmetria and flutter in showing predominantly truncal signs and in having a transient course. It differs from other forms of opsoclonus in not having the continuous and chaotic movements of the eyes characteristic of this latter entity. Nevertheless all these conditions have in com-

mon bizarre ocular oscillations that have to be seen to be appreciated.

Toxicology

Dr. Grant's book "Toxicology of the Eye" was published at a time (1962) when public and official concern over adverse side effects of drugs, including those on the eye, and adverse effects of environmental polutants and insecticides were just starting to expand. Now, Congressional action has caused various governmental and professional agencies to become much more concerned and to give much more attention to such factors, including those involving the eye. Reports on adverse effects on the eyes have appeared in rapidly growing number in the last few years, and awareness of these effects has spread widely through medical and related professions. Certain drugs have been banned from use in this country on the basis of toxic effects on the eyes, and warnings have been issued concerning many other drugs and chemicals. During this period, as a public service, Dr. Grant has maintained an information center on toxicology of the eye, and has responded to numerous requests for information on specific subjects from the Food and Drug Administration, National Institutes of Health, National Research Council, Congressional Investigational Committees, American Medical Association and industrial and private physicians.

Toxicologic research on the eye has been carried out by Drs. Grant, Thoft, Houle, and Meyer on substances suspected of having adverse effects in Glaucoma, by Dr. Michon on poisoning of the lens by miotic drugs, and by Dr. Kuwabara on poisoning of the retina by iodoacetate.

A survey of patients under long term treatment with psychotropic drugs was made by Dr. Alfred Scott and Dr. Grant. Incidentally, Dr. Grant has observed that annoying blurring of vision and interference with reading which is a side effect of atropine-like drugs used in conjunction with psychotropic medications can be conveniently and practically alleviated by applying a drop of a low concentration of long-acting cholinesterase inhibitor every couple of days to the patients' eyes. This is more convenient, cheaper, and more practical for young patients under treatment for mental illness than requiring them to put on reading glasses.

Virology and Immunology

Viruses, keratitis, and rabbits

The virology laboratory operated by Dr. Nesburn and supported by the NIH Center Grant has applied much of its research activity to a study of virus disease in rabbits. Like human beings, rabbits may show long-lasting spontaneous recurrences of keratitis many months after the primary infection has cleared. Contrary to common belief this is relatively frequent, having occurred in a third of the rabbits in the present study, and indicates the need for caution in evaluating agents such as epinephrine which are stated to cause reactivation of viral keratitis.

Work is nearing completion on characterizing a newly reisolated herpes virus of rabbits. This virus, which was last isolated in 1936, shows many characteristics of both the herpes viruses and cytomegaloviruses which up to this point have been distinct and easily separable. Especially significant from the practical point of view is the fact that this virus produces changes identical to those of herpes simplex virus in rabbit kidney cultures and false "positives" may result if rabbit tissue cultures are employed in the isolation.

Corneal graft reactions

To circumvent rejection of transplanted tissue, immunologists have in recent years found systemic administration of "Imuran" highly efficacious. But this drug is also highly toxic when given over long periods of time and Drs. Elliott and Leibowitz have explored various alternative methods of treatment in the hope of maintaining clear corneal grafts in experimental animals. Topical "Imuran" therapy was ineffective. On the other hand short term "Imuran" and prolonged topical steroid therapy was very promising. Systemic hydrocortisone alone was also found to be highly efficacious.

Preliminary observations were also made on azathioprine, another immunosuppressive agent. Since this might be useful in the field of corneal transplants the initial study was directed toward determining what adverse effects it might have on corneal wound repair. It was, in fact, found to reduce the tensile strength of corneal wounds significantly in experimental animals.

Cytology of hypersensitivity reaction

Collaborating with Dr. Martin Flax (Department of Pathology, Massachusetts General Hospital), Dr. Elliott made a study of the cytologic changes occurring with ocular hypersensitivity. After intracorneal injection of protein antigens sequential morphologic changes occur at the limbus and in the cornea that correlate with opacification of the cornea and suggest the local cellular sites of antibody formation.

Instrumentation

Measurement of the depth of the anterior chamber is frequently desirable, especially in cases of narrow angle glaucoma and in vitreous block. An attempt was made to use the split-ocular which Dr. Donaldson had previously designed for measurement of the corneal thickness but this was unsuccessful due to the obliquity of the beam. Dr. Donaldson has, therefore, constructed a new instrument which attaches to the slit lamp and incorporates the principle of doubling the slit beam. This instrument is simple to use and gives a reproducible measurement of the distance between the apex of the cornea and the lens.

Another innovation from Dr. Donaldson this past year has been the design and construction of a pointer to use in connection with projection of three dimensional photographs. Conventional pointers appear on the surface of the screen rather than within the picture. With the new hand held unit it is possible to project a pair of polarized images of an arrow so that they appear at any depth within the projected stereoscopic photograph.

TEACHING AND LEARNING

The Howe Laboratory staff is involved in teaching at all levels of ophthalmology. Its members participate in Dr. Alfred Scott's highly successful course for undergraduates, in Dr. Henry Allen's time-tested postgraduate courses, and most particularly in the pre-residency and post-residency fellowship programs.

With the idea that teachers, too, may profit from being taught, a "teach-in" was organized this past year for the faculty of the

undergraduate students. This first session, which featured Dr. Kuwabara's electron microscopy of the eye, generated sufficient enthusiasm to warrant repetition at regular intervals.

Dr. Reinecke, whose text "Refraction" was the basis for the first programmed course in ophthalmology, has now prepared, with Dr. David Miller, a similarly programmed text on strabismus and is preparing a still further text, this time with Dr. Jeremy Whitney, on ocular anatomy. For this latter, 8 millimeter films are being used with special projectors to be adapted to teaching machines for auto-instruction.

In the past Dr. Donaldson has made available collections of standard slides and descriptive syllabi from his stereoscopic collection of photographs representing neuroanatomy of the visual pathways, gonioscopy, corneal dystrophies and ocular manifestations of systemic disease. This past year he has prepared for more formal publication the first of a series of atlases which will cover the field of external diseases of the eye. This first atlas comprises 105 stereoscopic photographs illustrating congenital ocular anomalies and ocular manifestations of systemic disease.

The use of three dimensional photographs is an invaluable aid for teaching students. In the past this has been carried out either by individual viewers or by screen projection with the aid of polarizing glasses. Neither method is convenient for groups of three to six observers. For groups of this size Dr. Donaldson has made a compact table model which provides an image about a foot in size giving an excellent stereoscopic effect when viewed with polarizing glasses.

Our continuing interest in the didactic aspects of neuro-ophthalmology was further consolidated this past year by publication of a text "Neurology of the Visual System" by Dr. Cogan. This text, together with its companion "Neurology of the Ocular Motor System" which was published just 20 years ago, comprise the accumulated experience and notes which it has been our good fortune to develop in the Howe Laboratory.

While all Eye Residents are encouraged to have inquiring minds and to carry on investigational projects, certain ones who have teaching and research in ophthalmology as their principal and ultimate goal have been offered the opportunity of support through a Training Grant from the United States Public Health Service

to spend a year or two full time in research before starting their clinical residencies, and to carry on their research part time during the three years that they are clinical residents. This is the tenth year of this program. It was instituted by Dr. E. B. Dunphy, carried on for the last five years by Dr. Kupfer, and is now being administered by Dr. Grant. A recent review of the whole program since its inception provides evidence that it has very well achieved its purpose of providing specially trained individuals for research, teaching and public service in ophthalmology. Also, the research works which have come out of it are impressive. In most instances the Trainees have worked under supervision of full time members of the Howe Laboratory staff, but many Trainees have developed as self-reliant investigators, profiting mainly from informal associations with members of the laboratory staff, rather than requiring much formal direction or supervision. There have been relatively few disappointing participants in the program. The majority have graduated to very responsible positions of research, teaching, or public service in ophthalmology. The Howe Laboratory has indicated its interest and willingness in carrying on with this Training Program if the Public Health Service wishes to continue to offer its financial support for it.

Howe Library and Vision Information Center

The Howe Library, under the dedicated stewardship of Mr. Snyder, served approximately 10,000 reader-visits and circulated about 5,000 book or periodical items in the past year. Along with the rest of the Laboratory operations, it suffers from severe space problems and a particular stringency in finding places for new books.

A number of precious book items were given to the Library by Dr. Paul A. Chandler from the George A. Derby collection. These include such rarities as the first edition of Helmholtz' "Handbuch der Physiologische Optiks" published in 1867, the second edition of Georg Bartisch's "Augendienst" published in 1686, and two copies of the first edition of George Frick's "Diseases of the Eye" which was the first text book on ophthalmology authored by an American and published in the United States (1823).

After considerable deliberation we have accepted the govern-

ment's invitation to establish a Vision Information Center in the Boston area. In partnership with Harvard's Countway Library we hope to serve a national need for literature retrieval and to pioneer new methods of information communication in the field of vision. The Vision Information Center is part of the plan for decentralization of specialized branches within the National Library of Medicine and is the fourth such center to have been established. The other three represent Brain Sciences, Parkinson's disease, and Speech and Hearing.

The strictly bibliographic aspects will be centered at the Countway Library under the supervision of Mr. Ralph Esterquest. A glossary will be established and the literature references stored in a computer. The scientific aspects will be centered at the Howe Laboratory or Infirmary under the supervision of Drs. Cogan and Reinecke. The function of this aspect will be to inaugurate methods for the most expeditious dissemination of information relevant to vision.

How much will be accomplished by this Center remains to be seen. We all feel that present methods for literature retrieval and assimilation are inadequate and we are hopeful that new methods may mitigate the overwhelming pressure of trying to keep up to date. At least we think it is worth a try and feel pleased, however immodestly, that we were asked to make the attempt.

ORGANIZATION AND SERVICE

Photographic laboratory

The functions of the photographic laboratory have been considerably expanded this past year. Mr. Roger Lancaster is the photographer in charge and Dr. Donaldson is the staff supervisor. A Zeiss fluorescein photographic unit has been added to the equipment and numerous retinal angiograms have been recorded by Dr. Haining.

Personnel

Because approximately half of the Laboratory staff are customarily on fellowship or other training status, we are accustomed to perennial change-over of personnel. Never a happy occasion,

we have been resigned to it as a necessity serving the common good.

In addition to the usual fellowship exodus several senior staff members have taken up posts elsewhere these past two years. Dr. Ephraim Friedman is now Chairman of the Department at Boston University. Dr. Carl Kupfer is Chairman at the University of Washington. Dr. James Elliott is Chairman at Vanderbilt University. And Dr. Simmons Lessell has been appointed Acting Chairman of the Ophthalmic Service at the Boston City Hospital. Dr. Abraham Spector left to become Chief of Ophthalmic Biochemistry at Columbia University. Dr. Sidney Futterman will head the ophthalmic biochemistry laboratory at the University of Washington and Dr. John Andrews will inaugurate an ophthalmic biochemistry laboratory at Vanderbilt. Dr. Selma Hayman has joined the Institute of Cancer Research at Philadelphia.

Dr. Peczon has rejoined affiliated services of the Laboratory to assist Dr. Grant in the operation of the Glaucoma Consultation Service. In the biochemistry division Dr. Reif has joined the Laboratory to pursue the study on enzyme induction in retinal tissue culture and Dr. Jedziniak to compare metabolic processes in the red blood cell and in the lens.

With these change-overs one is reminded of an inscription over an archway to Harvard Yard which asserts on the entrance side "Enter to Grow in Wisdom" and admonishes on the departure side "Depart, Better to Serve Thy Country and Thy Kind."

Honors and Invited Lectures

Dr. Kuwabara was awarded an honorary M.A. degree by President Pusey at a recent faculty meeting. Dr. Kupfer was Visiting Professor for two months to the Department of Anatomy, University College, London. While there he pursued collaborative research with Dr. John Downer noted elsewhere in this Report. Dr. Kupfer was also guest lecturer of the Colorado Ophthalmological Society. Dr. Cogan was guest lecturer of the Canadian Ophthalmological Society and of the Canadian Medical Association and a Delegate to the Conference on Education in the Neurological Sciences at White Sulphur Springs. He and Dr. Kuwabara were also invited participants in the Retinal Symposium

at the 20th International Congress of Ophthalmology, held this past year in Munich, and at the dedicatory exercises of the Stein Institute in Los Angeles. Mr. Synder was similarly an invited participant at the 20th International Congress for the History of Medicine in West Berlin where he presented a report on "The Eyes of Theodore Roosevelt."

Support

In expressing our deep appreciation to the many friends for their support of the Laboratory we are perennially plagued by the fear that we do not sufficiently transmit our feeling of gratitude. It would be simple if we could say that such and such a gift was totally and independently responsible for a specific discovery, or that one single donation effected a specific cure. This would, of course, be unrealistic. In fact we much in all conscience discourage gifts for narrowly defined projects and have declined such contract assignments. Our function, as we see it, is not contractual research but rather the provision of an atmosphere in which good research thrives. Fortunately most of our benefactors understand this.

So, in thanking the many individuals and organizations who contributed generously to the Laboratory this past year we are grateful not only for the support but especially for the freedom in which the support was given, freedom to pursue whatever lines the investigators deem most profitable for the better understanding of vision, the eye, and causes of blindness.

The government and particularly the National Institutes of Health and the Atomic Energy Commission have been, of course, our most substantive supporters. We could scarcely operate without their munificent help. But there are many things which the built-in restrictions of government subsidy cannot effect and so we are heavily indebted to private sources for their inestimable assistance. We are particularly grateful this past year for the aid of the Massachusetts Lions Clubs who helped us pioneer some aspects of electron microscopy of the eye which would not have otherwise been possible. We are indebted to the Contract Bridge League which supported our efforts to push forward a glaucoma educational program. We are indebted to the Genrado Trust, to

Research to Prevent Blindness Inc, to the Devonshire Associates, and to the Shamroth Family Charitable Trust for their unrestricted gifts. And we are indebted to the many individuals who included the Howe Laboratory as part of their annual benevolences or as memorial gifts. We would particularly like to acknowledge the spirit that came with a gift from several very young ladies of North Andover who ran a successful carnival and chose to invest the net profit of $3.25 in eye research.

For General Expenses

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Electron microscopy of retinal dehydrogenases
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Research Career Development Award
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Control of intraocular pressure
Projection of the human retina on the lateral geniculate nucleus
Retinal metabolism
Corneal lipids
Ocular hypersensitivity

Finally, it is again a pleasure to acknowledge the willing cooperation of the following secretaries, technicians, and others who provided essential supportive services this past year: Margaret M. Acheson-Donato, Sarah R. Adams, Inez M. Berry, Barbara D. Bridgman, Marion O. Cameron, Anne Chapman, Andrew A. Cloutier, Elizabeth E. Colley, Mary Jo Dangerfield, Marie Davenport, Helen A. Day, Elias Dikmak, Josephine Donohue, Victoria Fischer, Cynthia R. Full, Christa Getz, Heidi Gilliam, Susan Hall, Margaret J. Harmon, Ellen M. Henson, Diana Hyams, Robert C. Kasabian, Dixie W. Kaslick, Mary Klein, Roger C. Lancaster, Lucy Lepreau, Alfred Ley, Irod Lindsay, Thomas P. Lloyd, Agnes Love, Domenic Magno, Anna Marchurs, Audrey C. Melanson, Gloria J. Merola, Charles Mokeler, Werner Mueller, Jr., Judith Mumma, Donna M. O'Neil, Diane Olmstead, Joann E. Perkins, Wanda Pilarski, Peter Poulimenos, Ellen Rammelkamp, Helen E. Rayen, Mireille Reverdin, Barbara E. Rosenberg, Marjorie E. Saunders, Judith G. Schwerdt, Frances Shapiro, Laura Strong, Rosemary Sullivan, Malcolm W. Swan, Bill H. C. Tung, Ann A. Waitkus, Olga Wehm-Dalton, Elizabeth M. Whitley.

David G. Cogan, M.D.
Director

HOWE LABORATORY PUBLICATIONS

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Aqueous humor dynamics. Series of lectures, Postgraduate Course in Ophthalmology, Harvard Medical School, 1966.

CARROLL, J. M.

Postgraduate Course in Ophthalmology, Harvard Medical School: Metabolism and nutrition of the cornea, September 8, 1966. Scleral contact lenses, October 20, 1966.

Therapeutic uses of scleral contact lenses. American Optometric Association, in Bloomington, Indiana, October 2, 1966.

COGAN, D. G.

Neuro-opthalmology Symposium, University of Miami, in Miami, Florida, January 3–7, 1966

Myasthenia gravis

Ocular muscle abiotrophies

Pathophysiology of human visual disorders. Seminar in Basic Neurological Sciences, Series III, The Visual System. Harvard Medical School, February 23, 1966.

Retinal vessels. Wills Eye Hospital, in Philadelphia, Pennsylvania, April 14–16, 1966.

Some ocular manifestations of metabolic disease. Division of Neurology, University of Virginia School of Medicine, in Charlottesville, Virginia, April 18, 1966.

Ocular findings in a case of Farber's lipogranulomatosis. Alumni Association of the Massachusetts Eye and Ear Infirmary, May 9, 1966.

Canadian Ophthalmological Society, in Jasper, Alberta, June 13–14, 1966:

Congenital ocular motor apraxia, retrospective study.

Congenital nystagmus.

Ocular correlates of inborn metabolic defects. Canadian Medical Association, in Edmonton, Alberta, June 16, 1966.

Summary of the current professional status and projected role of the National Eye Institute. Panel on Changing Roles and Responsibilities of National Agencies. Annual Meeting, National Committee for Research in Ophthalmology and Blindness, in Chicago, Illinois, June 26, 1966.

Retinal vessels: Anatomy. Symposium on Retinal Circulation.

XXth International Congress of Ophthalmology, in Munich, Germany, August 16, 1966.

Neuro-ophthalmology. Lecture to the Third Year Class, Harvard Medical School, September 28, 1966.

Ocular motor abnormalities. Series of lectures to the Postgraduate Course in Ophthalmology, Harvard Medical School, October 1966.

Congenital nystagmus. Phoenix Ophthalmological Society, in Phoenix, Arizona, November 1, 1966.

with Kuwabara, T.: The mural cell in perspective. Jules Stein Eye Institute, in Los Angeles, California, November 3–5, 1966.

Some types of ocular oscillations. Chicago Ophthalmological Society, in Chicago, Illinois, December 19, 1966.

COLLIS, W. J.

Neuroanatomy. Series of lectures to Postgraduate Course in Ophthalmological, Harvard Medical School, September-October 1966.

DONALDSON, D. D.

The Wilmer Institute, Johns Hopkins Hospital, in Baltimore, Maryland, April 1–2, 1966:

Congenital diseases.

Eye manifestitations of systemic disease.

Cataracts.

The eye as a window to systemic disease. W. W. Bakus Hospital Medical Staff, in Norwich, Connecticut, April 12, 1966.

Clinical diagnosis of lid lesions. Second International Symposium. Manhattan Eye and Ear Infirmary, in New York City, May 16, 1966.

Descemet's membrane tubes. American Ophthalmological Society, in White Sulphur Springs, West Virginia, May30–June 2, 1966.

Lesions of the optic nerve head. Maine Medical Society, in Rockland, Maine, June 13, 1966.

Series of lectures to the Lancaster Courses, in Waterville, Maine:

Sensory neuro-ophthalmology, July 4–9, 1966.

External diseases of the eyes, July 11–13, 1966.

University of Rochester Graduate Course in Ophthalmology, in Rochester, New York, July 19, 1966:

Foreign bodies involving the anterior chamber.

Congenital anomalies in the anterior segment of the eye.

Ocular photography and external diseases. University of Pennsylvania Postgraduate Course, in Philadelphia, Pennsylvania, September 26–27, 1966.

Techniques and diagnoses in gonioscopy. American Academy of Ophthalmology and Otolaryngology, in Chicago, Illinois, October 17–19, 1966.

Monthly Clinical Conferences, New England Ophthalmological Society, October 1965 to April 1966.

House Officer Lectures, Massachusetts Eye and Ear Infirmary:

Lid tumors, July 21, 1966

Lesions of the chamber angle, October 25, 1966.

Postgraduate Course in Ophthalmology, Harvard Medical School. Series of lectures, September to November 1966:
Neuro-ophthalmology; tumors of the iris and ciliary body; corneal dystrophies; anterior chamber; and systemic diseases.

ELLIOTT, J. H.

The ocular media. Lecture to the Third Year Class, Harvard Medical School, January 5, 1966.

Suppression of the corneal graft reaction by antimetabolite therapy. Association for Research in Ophthalmology, in Charleston, South Carolina, March 24–26, 1966.

Chemotherapeutic immunosuppression of the corneal graft reaction. Ophthalmology Staff, Vanderbilt Medical School, in Nashville, Tennessee, March 28, 1966.

Influence of antimetabolites on corneal wound healing. Ocular Immunology and Bacteriology Group, in Los Angeles, California, April 28–29, 1966.

Influence of azathioprine on healing of avascular stromal wounds. Alumni Association of the Massachusetts Eye and Ear Infirmary, May 11, 1966.

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GORN, R.

Physiology of retinal light damage. Alumni Association of the Massachusetts Eye and Ear Infirmary, May 10, 1966.

GRANT, W. M.

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Pharmacology of the eye, December 20, 1966.
Laboratories, October 18 & 25, 1966.

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Discussion of the paper "Steroids and glaucoma" by M. Armaly, New England Ophthalmological Society, November 16, 1966.

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Haining, W. M.

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Technique of fluoangiography and applications. Postgraduate Course in Ophthalmology, Harvard Medical School, December 13, 1966.

Hepler, R. S.

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Hutchinson, B. T.

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Angle recession glaucoma. House Officer Lecture, Massachusetts Eye and Ear Infirmary, August 25, 1966.

Postgraduate Course in Ophthalmology, Harvard Medical School, September to December, 1966: Series of lectures on glaucoma, refraction and fields.

Ocular anatomy lectures. Simmons College, December 1966.

Ophthalmic Assistants Program, Massachusetts Eye and Ear Infirmary. Series of lectures, September to December 1966.

Kinoshita, J. H.

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Polyol synthesis in the lens. Departments of Biochemistry and Ophthalmology, Columbia University, in New York City, May 11, 1966.

Further studies on galactose cataracts. Third Ophthalmic Biochemistry Conference, in Woods Hole, Massachusetts, June 19, 1966.

Osmotic effects of dulcitol retention in galactose cataract. International Symposium on Eye Biochemistry, in Tutzing, Germany, August 10, 1966.

Symposium on Membrane Transport and the Eye, Yale Medical School, in New Haven, Connecticut, October 3–4, 1966:

Biochemical requirements of the transport mechanism.

Changes in the ion transport mechanism in galactose cataract.

Biochemistry of a cataract. Department of Biochemistry, University of Oregon, in Portland, Oregon, November 7, 1966.

Postgraduate Course in Ophthalmology, Harvard Medical School, Fall 1966: Series of lectures on biochemistry of the lens, cornea and retina.

Kroll, A. J.

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Kupfer, C.

Transneuronal atrophy in the lateral geniculate nucleus of monkey. Institute of Ophthalmology, in London, England, January 26, 1966.

Recent advances in ophthalmic biochemistry. Residents and Staff, St. Thomas' Hospital, in London, England, January 26, 1966.

Outflow resistance in monkey and man. Manhattan Eye, Nose and Throat Hospital, in New York City, March 14, 1966.

Colorado Ophthalmological Society, in Denver, Colorado, March 19, 1966:

Gonioscopic appearance of the anterior chamber angle during the first year of life.

Gonioscopic diagnosis.

The mechanism of transneuronal atrophy in the lateral geniculate nucleus of monkey. Neurophysiology Seminar, Department of Biology, Massachusetts Institute of Technology, April 5, 1966.

Division of Ophthalmology, Yale University School of Medicine, in New Haven, Connecticut, June 10, 1966:

Embryology of the anterior chamber angle in man.

The determination of pseudofacility in monkey.

Kuwabara, T.

Fine structure of the retina. Pathology Department, Massachusetts General Hospital, January 11, 1966.

Retinal pathology. Seminar on Visual Science, Harvard Medical School, February 23, 1966.

with Gorn, R.: An electron microscopic study of retinal damage by light. Association for Research in Ophthalmology, in Philadelphia, Pennsylvania, April 1, 1966.

Pathogenesis of retinal angiopathy. Clinical Diabetes Association of Rhode Island, in Providence, Rhode Island, April 13, 1966.

Light damage of the retina (electron microscopic study). New England Ophthalmological Society, May 10, 1966.

Pathology of the endothelial damage. Cornea Symposium, in Andover, Massachusetts, May 13, 1966.

Light damage of the photoreceptic organ of the retina. Columbia University, College of Physicians and Surgeons, in New York City, May 17, 1966.

Fine structure of the eye. "Teach-in" of the Faculty of Ophthalmology, Harvard Medical School, June 5, 1966.

Fine structure of the eye. Lancaster Courses in Ophthalmology, in Waterville, Maine, June 26–28, 1966.

Membranous transformation of photoreceptic cell by light. Sixth International Congress of Electron Microscopy, in Kyoto, Japan, August 29, 1966.

Retinal pathology by light exposure. Retina Seminar, Osaka City University, in Osaka, Japan, September 1, 1966.

Vascular change in diabetes. Ehime Medical Education, in Matsuyama, Japan, September 4, 1966.

Retinal glia and horizontal cell. United States-Japanese Seminar on

the Fine Structure of the Retina, in Fukuoka, Japan, September 8–10, 1966.

Anatomy of the retinal vessel. Jules Stein Eye Institute, in Los Angeles, California, November 3, 1966.

with Poulimenos, P.: Iodoacetic acid poisoning of the retina. Association for Research in Ophthalmology, in Chicago, Illinois, October 13–15, 1966.

Histochemistry and fine structure of the eye. Postgraduate Course in Ophthalmology, Harvard Medical School, October 31 and November 9, 1966.

LAMBERT, B. W.

Radiation and steroid cataracts. Postgraduate Course in Ophthalmology, Harvard Medical School, September 6, 1966.

LEIBOWITZ, H. M.

Chemotherapeutic immunosuppression of the corneal graft reaction. II. Combined systemic antimetabolite and topical steroid therapy. Ocular Immunology and Bacteriology Group, in Los Angeles, California, April 28–29, 1966.

with Elliott, J. H.: Suppression of immunogenic corneal graft rejection. New England Ophthalmological Society, May 10, 1966.

Chemotherapeutic immunosuppression of the corneal graft reaction. Cornea Conference, in Andover, Massachusetts, May 13, 1966.

LOU, M. F.

Control of glycolysis in lens. Third Ophthalmic Biochemistry Conference, in Woods Hole, Massachusetts, June 18–20, 1966.

MICHON, J., JR.

Cholinesterase in the lens. New England Ophthalmological Society, May 10, 1966.

Studies on the type and location of cholinesterase in the calf lens. Third Ophthalmic Biochemistry Conference, in Woods Hole, Massachusetts, June 18–20, 1966.

Effects of anticholinesterase agents on the lens. Association for Research in Ophthalmology, in Chicago, Illinois, October 13–15, 1966.

The influence of miotics on the lens. New England Ophthalmological Society, November 16, 1966.

NESBURN, A. B.

Introduction to ophthalmic virology. Postgraduate Course in Ophthalmology, Harvard Medical School, September 18, 1966.

with Laibson, P. and Carroll, J. M.: Recurrence of herpes simplex keratitis. New England Ophthalmological Society, December 21, 1966.

REINECKE, R. D.

Ophthalmologists, opticians, and optometrists. Profession Training Lecture to Ladies Visiting Committee, Massachusetts Eye and Ear Infirmary, March 9, 1966.

The ACA ratio and strabismus. House Officer Lecture, Wills Eye Hospital, in Philadelphia, Pennsylvania, April 14, 1966.

ACA nomograms. The Houston Ophthalmological Society, in Houston, Texas, April 21, 1966.

Corneal lacerations, treatment and prevention of synechia. Baylor University College of Medicine, in Houston, Texas, April 22, 1966.

ACA ratios and squints. Alumni Association of the Massachusetts Eye and Ear Infirmary, May 9, 1966.

A general introduction into the conditions and nature of eye diseases treated at the Massachusetts Eye and Ear Infirmary. Chaplin's Group at the Massachusetts General Hospital, June 1966.

Programmed refraction course. The Lancaster Courses in Ophthalmology, in Waterville, Maine, August 3–6, 1966.

Problems in strabismus, I and II. House Officer Lectures, Massachusetts Eye and Ear Infirmary, August 23 and 30, 1966.

Vision Information Center and programming. The New York Chapter of the National Society for Programmed Instruction, in New York City, December 14, 1966. ibid, The Boston Chapter of the National Society for Programmed Instruction, in Wellesley, Massachusetts, December 15, 1966.

SNYDER, C.

The eyes of Theodore Roosevelt. XXth International Congress for the History of Medicine, in Berlin, West Germany, August 25, 1966.

Studies on the literature of otolaryngology. Residents in Otolaryngology, Massachusetts Eye and Ear Infirmary, September 24, 1966.

The beginnings of the twin specialties — ophthalmology and otology. American Academy of General Practice, in Boston, Massachusetts, October 10, 1966.

The introduction of anesthesia into ophthalmology. Anesthesia Study Group, in Boston, Massachusetts, October 26, 1966.

STEPHENS, K. F.

Quantitated forced ductions. American Academy of Ophthalmology Otolaryngology, in Chicago, Illinois, October 18, 1966.

THOFT, R. A.

The rate of potassium exchange in normal and galactosemic lenses. International Symposium on Eye Biochemistry, in Tutzing, Germany, August 10, 1966.

Clinical aspects of meiotic therapy. New England Ophthalmological Society, November 16, 1966.

WORTHEN, D. M.

Experience with a simplified cryoextractor. Alumni Association of the Massachusetts Eye and Ear Infirmary, May 9, 1966.

Ophthalmic cryosurgery. International College of Surgeons, in Manchester, Virginia, July 4, 1966.

Ophthalmic cryosurgery. House Officer Lecture, Massachusetts Eye and Ear Infirmary, Fall 1966.

Zweifach, P. H.
House Officer Lectures, Massachusetts Eye and Ear Infirmary:
Visual fields, September 27, 1966.
Ocular motor palsies. November 17, 1966.

Exhibit

Kuwabara, T. and Cogan, D. G.: Retinal Vascular Patterns. XXth International Congress of Ophthalmology, in Munich, Germany, August 15–19, 1966.

FORM OF BEQUEST

The Howe Laboratory of Ophthalmology is an independent department of the Harvard Medical School and is jointly supported by a restricted endowment of Harvard University and by the Massachusetts Eye and Ear Infirmary.

For the information of those who may wish to contribute to this Laboratory, a form of bequest is here set forth:

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Such bequests are managed by the Treasurer's Office of Harvard University, and the income is accredited to the Laboratory.

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Michael L. Kern
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* Transferred to another institution during 1966.